robustness of the model by folding different WALP transmembrane helical peptides starting from stretched, unstructured conformations using both simple canonical simulations and enhanced-sampling techniques [4]. Finally, the method is used to fold the 50-residue-long major pVIII coat protein (fd coat) of the filamentous fd bacteriophage. The results show excellent agreement with experimental structures and atomistic simulations in implicit membrane, demonstrating that such a protocol can serve as a starting point for better-refined atomistic simulations in a multiscale framework.

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**1252-Pos Board B203**

**Opening the Lateral Gate of the Rhomboid Protease Couples to Lipid Binding**

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Rhomboid intramembrane proteases dock and cleave transmembrane substrates within the lipid bilayer. The conformational dynamics of the lipids, substrate and rhomboid during substrate binding are poorly understood. A particularly important question is whether during substrate binding the protease must open a lateral gate - its transmembrane helix 5 - toward the lipid bilayer, and if so how opening of the lateral gate couples to rearrangements of the surrounding lipids.

Experiments on the Hemophilus influenzae GlpG have identified mutations that either promote or inhibit the catalytic activity of the protease. We thus reasoned that understanding the conformational dynamics of active vs. inactive rhomboids can give insight into the motions compatible with productive substrate binding. We performed prolonged all-atom simulations of wild type and mutant H. influenzae GlpG for time scales of up to ~250ns. We find that, relative to the wild type, in a triple mutant with enhanced catalytic activity the gate helix 5 displaces laterally. This displacement creates an opening at the substrate-docking site that lipid molecules fill. The strong coupling between lipid and protease dynamics revealed by the simulations suggests that lipid dynamics can shape the energetics of substrate binding to the active site.

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**1253-Pos Board B204**

**High Resolution Model of HDL Wrapped with Tetrafoil apoA-I: A Coarse-Grained Simulation Study**

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High density lipoproteins (HDL) prevent the formation of plaques in arteries by transporting excess cholesterol from peripheral tissues to liver for excretion. Hence, elevated levels of HDL is vital in controlling the progression of cardiovascular diseases (CVD). Inspite of HDL's preventive role in CVD, very less is known about its structure and function. Recent chemical cross-linking and mass spectrometry studies revealed that the core structure of HDL is wrapped by three to five apoA-I proteins, which influence the binding of various metabolic enzymes like LCAT and CETP.[1] A sophisticated model of HDL wrapped with four to five apoA-I chains is still missing in the literature, although some effort has been put forward to design the structure of HDL wrapped with smaller number of apoA-I chains.[2] In the present work, we propose a model of HDL that resembles the experimentally measured composition of POPC, PPC, cholesterol, cholesteryl ester and triglyceride molecules. The self-assembled droplet from coarse-grained simulation was subsequently wrapped with four apoA-I chains (*tetrafoil* model) and reverse transformed. The lipid-protein interactions and the structural organization of lipids in HDL were analysed through multi-microsecond coarse-grained and united atom simulations. The model is validated by reproducing various experimentally determined properties, such as the density of HDL, apoA-I chemical cross links, diffusion coefficients of lipid fractions and order parameter of lipid acyl chains.

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**1254-Pos Board B205**

**Membrane Association of Synaptotagmin 7 C2A Domain by Molecular Dynamics Simulations**

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Synaptotagmin (Syt) acting as a calcium sensor promotes SNARE-mediated membrane fusion by docking to target membrane. Here we study the C2A domain of Syt7, which triggers $Ca^{2+}$-dependent release of large dense-core vesicles in several cell types, by doing atomistic molecular dynamics simulations and Poisson-Boltzmann calculations. The association of the Syt7 C2A with membrane (POPC:POPS=3:1) was found accompanied by seesaw-like movements of the protein, primarily due to two significant interactions: (1) the electrostatic attractions between the negatively-charged lipid headgroups and the positively-charged residues in the loops L1-L3 and (2) the hydrophobic interactions between the lipid tails and a critical phenylalanine residue F167. Good linear correlation was found between the EPR measured penetration depth parameters and the theoretically calculated average penetration depths for a large number of residues.

**1255-Pos Board B206**

**Interplay between Electrostatics and Cation-PI Interactions Governs the Specific Membrane Binding of Phosphatidylinositol-Specific Phospholipase-C**

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*Bacillus thuringiensis* phosphatidylinositol-specific phospholipase C (*Bt*PI-PLC) is an amphitropic enzyme which cleaves GPI-anchored proteins off the outer surface of eukaryotic plasma membranes. Amphitropic proteins bind specifically and transiently to the surface of cell membranes, and their functions are regulated upon binding. It is commonly acknowledged that non-specific electrostatic forces are responsible for their long-range interactions with membranes. Using continuum electrostatics calculations we show how, despite having an overall negative charge (−7e), the charge distribution of *Bt*PI-PLC leads to favorable electrostatic interactions with anionic membranes. However, the resulting electrostatic binding free energy, which is essential for membrane binding, is quite low. Mutation of a single, key basic residue to alanine diminishes this long range electrostatic contribution making it difficult for *Bt*PI-PLC to associate with membranes. Once close to the membrane surface, short range non-specific hydrophobic interactions and specific cation-pi interactions with the $N(Me)_3$ groups of phosphatidylcholine (PC) lipids of the membrane likely come into play for *Bt*PI-PLC binding to the membrane surface. 500ns-long all-atom molecular dynamics simulations of *Bt*PI-PLC docked to mixed bilayers with varying ratio of zwitterionic lipids indeed confirm this. Finally, we see that the interplay between long range electrostatics and short range, PC specific cation-pi interactions governs the specificity of *Bt*PI-PLC for PC rich membrane. Moreover, our results show that *Bt*PI-PLC can achieve favorable electrostatics interactions with lipid bilayers without having surface-exposed basic clusters suggesting that such clusters are not always necessary for the regulation of amphitropic enzyme binding.

**1256-Pos Board B207**

**Molecular Details of the Mechanism of PS Recognition by TIM Proteins**

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Accumulating evidence suggests that an immune response can be triggered by the presence of abnormal lipid components, such as phosphatidylserine (PS), in the outer leaflet of the cellular membrane. The T-cell immunoglobulin and mucin domain (TIM) family of proteins recognize PS exposed on the surface of the membrane. TIM proteins are expressed by numerous cell types, and despite their close structural similarity, they are involved in triggering different immune responses. These specific roles have been attributed to different factors, including differential binding modes of TIM proteins to anionic membranes and their variable sensitivity to lipid composition of the membrane.

In order to study the mechanism of membrane binding by TIM proteins, we have performed MD simulations of TIM1 and TIM3 employing our